HUSBANDRY OF THE NEONATE

CHAPTER 6

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The word *husbandry* comes from Old English and means caretaker, manager, or provider. At no other period in an organism's lifetime is it more dependent nor does it require more care and protecting than when it is a neonate. Newborns have many unique physiologic characteristics that are in an active state of transition, as well as anatomic, nutritional, and behavioral deficiencies that distinguish them dramatically from adults. Newborn animals are complicated, but if they are approached in a uniform, systematic fashion their therapy can be extremely rewarding.

Proper neonatal husbandry must include a variety of considerations. Some sources claim birth defects in mammals approach 16%, whereas others claim a 20% fatality rate for puppies in the first 2 weeks of life. This chapter considers newborns from birth to weaning by close examination of their idiosyncrasies (Box 6-1).

THERMOREGULATION

Neonatal animals are poor regulators of their body temperature. Newborns can lose body heat because of evaporation, radiation, convection, and cooling. If newborns are wet or placed next to cold objects (cage or kennel floors), in drafts, or in outdoor enclosures, they can lose considerable amounts of heat. Orphaned newborn puppies during their first week of life require environmental temperatures of 85° to 90° F (30° to 32° C).

For puppies, newborns have lower body temperatures than adult dogs. In the first week of life rectal temperatures range from 95° to 97° F (35° to 36° C), and for the second and third weeks temperatures range from 97° to 100° F (36° to 38° C). By the time of weaning, average rectal temperatures are nearly the same as those of adults.

Reflexes, such as shivering, and vasoconstrictive mechanisms to maintain heat are not developed in the neonate. Brown adipose tissue found in newborns is the site of nonshivering thermogenesis. Wet puppies, inappetent puppies, and orphaned newborns are thus unable to successfully maintain their body temperature in cool or drafty environments. Although shivering is absent in newborn puppies, panting is present in overheated neonates.

Maintenance of normal physiologic functions is related to temperature in puppies and kittens. In puppies that become chilled, the heart rate may drop precipitously. A newborn with a rectal temperature of 96° F has a heart rate somewhere between 200 and 250 beats per minute (bpm). Once the rectal temperature reaches 70° F, the heart rate quickly drops to only 40 bpm. A decreased heart rate may result in inappetence, dehydration, and loss of suckling reflexes. In addition, nursing bitches may refuse to nurse and care for cold puppies and even push them away. When body temperature falls below 94° F, a gastrointestinal (GI) ileus develops and a chilled puppy will stop trying to nurse. If chilled puppies are not rewarmed before force feeding, regurgitation and subsequent aspiration pneumonia can result (Box 6-2).

Hypothermia in newborns can, however, have a sparing effect. The hypothermia that results in decreased cardiovascular function may conversely protect puppies from the ischemic brain injury that accompanies cardiovascular collapse. In one investigation, induction of hypothermia resulting in circulatory onset of up to 1 hour was not responsible for subsequent brain injury. If hypothermia-related circulatory arrests lasting more than an hour were induced, neuronal injury resulted. In puppies with sustained hypothermia, tissue hypoxia, metabolic acidosis, and cell death all subsequently ensue.

The ability for lymphocytes to transform and combat infection is significantly decreased when pups are chilled. The cardiovascular and GI systems depend on body temperature, and the immune system is also closely influenced by a change of only a few degrees.

Warming chilled neonates back to normal temperatures can be potentially very dangerous. Newborns must be warmed safely after cooler body temperatures are discovered.

BOX 6-1 Significant husbandry issues for the neonate

- Sick neonatal animals should always be checked for hypoglycemia. Clinical signs of hypoglycemia in neonates include lethargy, failure to suckle, depression, mental dullness, stupor, tremors, and seizures. Hypoglycemic animals may also show agitation, vocalize, be irritable, be intensely hungry, and lose consciousness.
- Diarrhea in newborns can be a result of overfeeding, hyperosmolar diets, viruses, or parasites. Body temperature is critical in neonates. At body temperatures below 94° F (34.5° C) ileus develops. This decreases their ability to suckle and nurse and increases their chances for aspiration and pneumonia.
- Both feline and canine newborns are immunologically incompetent and antibody deficient at birth. Passive immunity is acquired through the adequate ingestion and absorption of maternal colostrum during the first 24 hours after birth. Ability for antibody absorption decreases markedly after 12 hours.
- If colostrum intake is not possible or available, pooled adult serum can be administered to puppies and kittens to elevate serum immunoglobulin concentrations (22 ml/kg and 15 ml per kitten). T-cell mitogenesis and differentiation and phagocytic cell functions are not fully mature until 12 to 16 weeks of age.
- When recommending vaccine regimens for young animals, veterinary clinicians must consider a number of important criteria. These include (1) the morbidity and mortality of the specific disease, (2) the prevalence or actual incidence rate of the disease, (3) actual risk of that individual for exposure to that disease, (4) efficacy of the vaccine, (5) risks associated with the vaccine, (6) any potential for zoonotic infection by that disease, and (7) route of infection and transmission by this disease.
- Based on consideration concerning these criteria, vaccines for puppies and kittens can be regarded by either "core," "noncore," or "not recommended." However, each animal must be assessed as an individual with all the benefits and risks evaluated before any vaccine can be administered.
- Clinical signs of neonatal septicemia include weakness, failure to suckle, diarrhea, hypothermia, cyanosis, vocalization, and finally coma. Sloughing of extremities (e.g., toes, tails, ears) can be observed.
- Treatment of failing newborns involves aggressive fluid support, combating septic shock, and nutritional buttressing. Selection of a safe, efficacious antibiotic may be required.

BOX 6-2 Effects of drop in body temperature on neonates

- Heart rate drops.
- GI ileus may result.
- Chilled neonates have less ability for lymphocyte transformation.
- Mothers reject newborns with cool skin.

GI, Gastrointestinal.

Heat sources must be safe, effective, and easily monitored. Warm water bottles wrapped in towels or cloth, boiled rice heated in a sock, or warmed towels can provide adequate heat but must be judiciously scrutinized. Water should be changed and reheated as it cools, since there is the risk of chilling newborns with cold bottles and containers full of cold water. Similarly, newborns are neurologically immature and lack the ability to move away from excessive heat. Cloth coverings or pillow cases can decrease direct contact of the delicate newborn skin with hot water bottles and heat sources, but these types of heat supplements can overheat, dehydrate, and even severely burn ill, comatose, or orphaned newborns. For these reasons, heating pads, heat lamps, and electric blankets are not recommended because they are so difficult to regulate and safely manage.

Pediatric incubators are easily available and are ideal in managing sick, debilitated, or orphaned puppies and kittens. Nevertheless, these devices can also lead to problems if not rigorously attended. Environmental control for newborns must also consider humidity. Use of incubators can lead to mucous membranes that are quickly dried out. A relative humidity of 55% to 65% is considered adequate for the prevention of skin drying. In neonatal, low birth weight puppies, relative humidity of 85% to 90% is most effective in maintenance of hydration and body temperature. If high humidity is provided, care must be taken not to reach environmental temperatures greater than 90° F (32° C). Temperatures of 95° F (35° C) and greater coupled with relative humidities of over 95% lead to respiratory distress in neonatal puppies and kittens. Oxygen cages are also an excellent way to warm newborns.

The best incubators, whelping boxes, or closed environments present the newborn with a gradient of temperatures and allow the puppies and kittens to select the most comfortable zones. Nevertheless, even healthy pups and kittens initially are neurologically immature and unable to move away from excessive heat.

REGULATION OF CARBOHYDRATES

Newborns differ substantially from adults with regard to their ability to maintain normal blood glucose levels. Ill neonates must always be evaluated for hypoglycemia. Hypoglycemia in the newborn can be due to a variety of causes and can appear in conjunction with hypothermia, sepsis, starvation, toxic milk syndrome, or any combination of these things. The capacity of the newborn for the regulation of blood glucose may be directly related to the nutritional state of the dam during pregnancy. Starvation of the mother can lead to lower birth rates, lower fetal blood glucose concentrations, and increased fetal ketone levels. Starvation of the mother also reduced fetal birth weight by 23% and resulted in significantly lower fasting blood glucose levels in pups at 3 hours of age when compared to controls in one study. Furthermore, bitches fed a low-carbohydrate diet had both a higher incidence of stillbirths and a higher incidence of neonatal losses in the first 3 days after whelping.

Neonates born to healthy, well-fed mothers are better able to maintain blood glucose for even several hours after the fast. However, since the neonatal liver contains minimal glycogen stores, even slight fasts can cause hypoglycemia. The neonate is born with limited capacities for gluconeogenesis and glycogenolysis because of the immaturity of the newborn's liver. In addition, initial limited hepatic glycogen stores, small muscle mass, lack of adipose tissue, and decreased use of free fatty acids as an alternative energy source place neonates at great risk for developing hypoglycemia in the face of even the briefest fast. Impaired gluconeogenesis caused by the delayed maturation and induction of the rate-limiting gluconeogenic enzymes has been shown to result in hypoglycemia in human infants and is suspected in the same condition in kittens and puppies.

Hypoglycemia of immature (less than 6 months old) toy and miniature dog breeds is frequently reported. Just as in human infants, alanine deficiency has been implicated in this condition in young dogs. The rate of alanine release from muscle determines the rate of gluconeogenesis during starvation. These toy breeds have much smaller muscle mass, immature enzymatic machinery, and smaller muscle stores to begin with, thus hypoglycemia develops more easily.

Hypoglycemic neonates have often been under extreme stresses; they have only recently been purchased or otherwise obtained and have had a huge change in their environment, as well as their diet. GI problems, anorexia, diarrhea, and vomiting are commonly reported. These signs may also be the result of parasites. Neonates lack the feedback mechanism between hepatic gluconeogenesis and blood glucose concentrations, making regulation of blood glucose much more difficult than for adult dogs, and a variety of other factors can lead to this hypoglycemia. In addition, a host of other conditions inherited, contracted, or acquired can cause hypoglycemia in newborns. Endotoxemia, sepsis, portosystemic shunts, and glycogen storage abnormalities have all been recognized as conditions that can cause a profound decline in blood sugar concentrations.

Inherited, inborn errors in amino acid and/or carbohydrate metabolism; inadequate protein, glycogen, or carbohydrate stores; and immature, deficient, or faulty enzyme systems should be considered in neonates with repeated bouts of hypoglycemia in the absence of any identifiable contagious cause (septicemia/endotoxemia). If hypoglycemia recurs in neonates with a good diet and adequate nutrition, glycogen storage disease should be suspected. Glycogen storage disease also might be considered if neonates with recurrent hypoglycemia episodes also display acidosis, ketosis, and hepatomegaly.

TABLE 6-1 Treatment of hypoglycemia in newborn dogs

Dextrose concentration (%)	Amount administered (ml/oz/dog)
5%	0.25-0.6525 IV
10%	0.125 to 0.31 IV
50%	0.25 to 0.625, orally, direct to gums. Never give higher than 10% IV.

IV, Intravenous.

Normal concentrations for blood glucose in neonates are considered to be 52 to 127 mg/dl for neonatal pups between the ages of 1 to 3 days and 111 mg/dl at 4 weeks of age. The normal adult range of blood glucose concentrations has been reported at 65 to 110 mg/dl. Blood glucose less than 40 mg/dl in pups 2 to 6 weeks of age should be considered abnormal, particularly if clinical signs are present.

Clinical signs of hypoglycemia in neonates include lethargy, failure to suckle, depression, mental dullness, stupor, tremors, and seizures. Accompanying signs may include agitation, vocalization, irritability, intense hunger, and loss of consciousness.

Treatment for hypoglycemia is initiated after a diagnosis has been made. Dextrose 0.2 to 0.5 gm/lb (0.5 to 1.0 gm/kg) can be administered *slowly* (over several minutes) intravenously through the jugular veins of most pups. Solutions of 5% to 10% dextrose are recommended for intravenous (IV) administration. Higher concentrations of dextrose may be directly applied to mucous membranes but should *never* be given intravenously because of the risk of phlebitis (Table 6-1). Because of the immature metabolic mechanisms in neonatal animals concerning glucose metabolism and the potential for inherited glycogen storage diseases, blood glucose levels should be determined before more dextrose is administered to a neonate who fails to respond to therapy.

HEPATIC AND RENAL CONSIDERATIONS

Veterinarians treating neonates must come to recognize the differences between adult animals and the immature liver and kidneys of newborns. These differences are critical in terms of drug metabolism and excretion. Nephrogenesis is not completed until the third week after birth. As cortical blood flow changes and as maturation of nephrons occurs, various parts of the kidney are vulnerable to drug toxicity at various times. Protein, glucose, and amino acids are higher in the urine of neonatal pups than in adult dogs. Nevertheless, urine specific gravity is usually lower. During the first 8 weeks after whelping, the urine specific gravity ranges from 1.006 to 1.017. At or about 8 weeks, the urine specific gravity of the neonate approaches that of an adult animal. Urination begins soon after birth. The dam stimulates the vulva or prepuce of the neonate in order to get the newborn to urinate. After a few weeks, they are urinating on their own.

A variety of functions of the liver are immature or incompletely developed in the neonate enzyme system such as the P450; reduction, hydroxylation, and demethylation are not fully mature until animals are at least 5 months of age. Drugs that are metabolized and excreted by the liver should be avoided in neonates or a modified dosage scheme should be developed. However, for many drugs, no such schemes or schedules are available.

CARDIOPULMONARY COMPETENCE (see Chapters 32 and 34)

Cutaneous stimulation and manipulation of a newborn puppy initiates a reflex respiration. This reflexive response can be seen when the bitch licks and nips the newborn or when surgery assistants rub puppies after cesarean section. Respiratory rates of adult dogs are 16 to 32 bpm. Respiratory rates of pups are 10 to 18 bpm during the first week of life, 18 to 36 bpm during the second week, and by the third week of life it becomes the same as the rate of adult dogs. Newborn pups respond to hypercapnia by reflexively increasing bronchomotor tone. However, a pulmonary response to hypoxia is either lacking or minimal. In pups, bradycardia can occur as oxygen partial pressure drops, quite unlike the tachycardia shown in response to hypoxemia by adult dogs. Veterinary clinicians must realize that hypoxemic neonatal pups may have heart rates expected for healthy adult dogs (this despite the fact that the heart rate of normal newborn pups is 200 to 250 bpm).

Baroceptors for blood pressure are operational by the fourth day of life. This causes the heart rate of pups to vary in reaction to changes in blood pressure just as occurs in adult dogs. Mean arterial blood pressure is between 30 and 70 mm Hg in 1- to 4-week-old pups, which is much lower than that found in adults. Blood pressure is affected by a multitude of factors, including body temperature and blood glucose concentration. For severely hypoglycemic pups, the mean arterial blood pressure may drop as much as 50%. After the first week, arterial blood pressure increases with age and reaches adult levels somewhere between 6 weeks and a few months of age. The electrocardiogram (ECG) of neonates is much different than that of adults. In one report, the QRS modal axis of the ECG switched from a right cranioventral direction in the first week after birth to a left caudoventral orientation 12 weeks after whelping. This significant cardiac axis change may represent the change in ratio of right ventricular to left ventricular mass. At birth, the mass of right ventricle relative to the left ventricle is 1:1 in neonates and 1:2 or 1:3 in normal, mature adult dogs. This change in mass is intimately reflected in the ECG.

NERVOUS SYSTEM (see Chapter 40)

The development, onset, and appearance of different neurologic reflexes vary tremendously in the newborn. The suckling reflex for nursing should appear within an hour of birth. Neonatal puppies and kittens can raise their heads and move by propelling themselves forward on their ventral thorax shortly after birth. Although flexion is the predominant posture of pups at birth, within the first 5 days, extensor muscles achieve dominance. Although eyes and ears do not open for almost the first 2 weeks, neonates do respond to noises and can show a slow blink to lights shined through closed eyelids.

Newborns have an immature blood-brain barrier. The gradient is permeable to lactic acid, which the body can utilize as a nutrient when starved or hypoglycemic. The immature nature of the blood-brain barrier of the neonate provides easier access for drugs into the central nervous system (CNS). Antibiotic molecules normally prevented from entering the adult brain can enter the brain of the neonatal puppy or kitten. Thus many drugs can achieve dramatic cerebrospinal fluid concentrations in the newborn. As a result, great care must be taken when drugs are administered to immature animals. Since a greater effect of the drug is possible, a greater potential for toxicity also exists. Tetracyclines, penicillins, sulfonamides, and a host of other drugs may obtain worrisome levels in the newborn CNS.

GASTROINTESTINAL SYSTEM (see Chapter 36)

The GI tract of neonates is sterile at birth. In the first few days, the GI tract is quickly colonized by microorganisms. Diet (whether nursing or bottle fed), environment, antibiotic therapy, or bacterial, viral, or parasitic disease can affect the rate of colonization.

Puppy and kitten GI tracts are well-developed at birth and produce a yellowish, semiformed stool while nursing. Care must be taken to note the stools of neonates. They are not always observed, since mothers ingest the feces of the newborn. Orphaned pups fed formula and puppies supplemented while nursing often develop diarrhea. Diarrhea may result from bacterial overgrowth, overfeeding, hyperosmolar diets, viruses, or parasites.

Estimation of the age of pups, even when pups are orphans, becomes important after recommending appropriate vaccination schedules. Age of newborns can be estimated by identifying the eruption dates of various deciduous and permanent teeth. Somewhere between 3 and 6 weeks deciduous teeth erupt and when this occurs, the dam encourages weaning of the newborns.

IMMUNE SYSTEM (see Chapter 14)

It has long been recognized that neonatal animals have immature immune systems. Little passive immunity is acquired by developing animals in utero; the majority of passive immunity is obtained after birth from the colostrum of the mother. Colostral antibodies are received during the first 24 hours postpartum and are primarily responsible for immunity during the first several weeks of life. After the first 24 to 36 hours, little further uptake of colostral antibodies occurs across the GI tract. However, although they are no longer absorbed, colostral antibodies in the milk continue to be protective by preventing infections that initiate from the oral or intestinal mucous membranes of the neonate. These antibodies, predominantly immunoglobulins (Ig) A (IgA) and IgG, provide some level of protection. In the mouth, esophagus, and oropharynx, IgB antibodies play a major role, whereas in the stomach and intestines, IgA antibodies are at work. The protection provided by colostral antibodies drops quickly so that between 6 and 20 weeks of age they are no longer functional.

Although colostral antibodies supply the majority of neonatal immune protection, newborns are able to mount some antibody response to various antigens. This neonatal response is produced mainly by IgM. The production of antibodies by B cells depends on the activity of T-helper cells. The humoral response of pups is immature when compared to that of adults. It is not known at present whether this is due to the immaturity of B- or T-lymphocyte lines.

At birth, proliferation of T cells induced by mitogens and various substances is minimal, which may explain the neonate's lack of response to early vaccination regimens and overall susceptibility to infections. Differentiation and maturation of T lymphocytes occurs in the thymus. In dogs, during the first 12 weeks postpartum, T lymphocytes increase over 200-fold.

In addition to B and T lymphocytes, other factors are necessary for a mature, operational, and fully functioning immune system. Enzymes, complement, and polymorphonuclear cells are all involved in the immune response of the young animal. In neonates, complement components can be deficient and phagocytic activity can be defective, leading to reduced killing of microorganisms, decreased phagocytosis, and defective opsonization of bacteria.

ANTIBIOTICS, DRUGS, AND NEONATAL ANIMALS (see Chapter 27)

In the husbandry and management of newborn domestic animals, veterinary clinicians must be aware of the special sensitivities of neonatal animals to certain antimicrobial drugs and only select drugs that are safe and effective. In this section, several drugs are examined that have been reported as unsafe in younger animals (Table 6-2).

Gentamicin sulfate is an aminoglycoside antibiotic. It is bactericidal and its mechanism of action is to inhibit bacterial protein synthesis by binding with the 30S ribosome. It is a broad-spectrum antibiotic, except for anaerobic bacteria and certain streptococci. Nephrotoxicity has been reported in pups and the young of several species. Animals must have adequate fluid and electrolyte balance if it is to be used. The much-described ototoxicity has not been reported in animals. It is a poor selection in animals with decreased or immature renal function.

TABLE 6-2 Antibiotic considerations in neonates

Drug	Considerations
Tetracycline	Known to chelate calcium. Results in abnormal teeth and bone development. Not for use in young animals.
Trimethoprim + sulfonamides	Known to cause arthropathy, anemia, skin reactions, and keratoconjunctivitis sicca. Not for use in young animals.
Gentamicin sulfate	Nephrotoxicity is the most drug-limiting toxicity. Ototoxicity and vestibulotoxicity also possible but have not been reported in animals. Not for use in animals that are dehydrated or that have compromised renal function, renal insufficiency, or renal failure. There must be adequate renal clearance present if gentamicin is to be used. Safer drugs are available for young animals.
Enrofloxacin	All of the fluoroquinolones can cause arthropathy in young animals. Dogs are most sensitive at 4-28 weeks of age. Large, rapidly growing dogs are most susceptible. High concentrations can cause CNS signs, especially in animals with renal failure. At higher dosages can cause nausea and diarrhea. Not for use in young animals.
Metronidazole	Most toxicities are dose related. Most animals showing neurotoxic signs have been receiving dosages over a prolonged period. At suggested dosages, fetal abnormalities have not been reported. However, metronidazole has been shown to be mutagenic and genotoxic in some species. As a result, it is not recommended during pregnancy.

CNS, Central nervous system.

Enrofloxacin is one of the fluoroquinolones. The antibacterial acts via inhibition of DNA gyrase in bacteria that inhibits DNA and RNA synthesis. Enrofloxacin is a broad-spectrum antibiotic and is metabolized to ciprofloxacin. Susceptible bacteria include *Staphylococcus, Escherichia coli, Proteus, Klebsiella,* and *Pasteurella*. It does not have good activity against anaerobic bacteria. All fluoroquinolones may cause arthropathy in young animals. It causes abnormal development in articular cartilage and causes destructive lesions in animals younger than 18 months of age. Rapidly growing, large, and giant breeds of dog appear most susceptible. Cats appear relatively resistant to cartilage injury. Cats at higher dosages may display retinal degeneration and subsequently develop permanent blindness. Injected solutions may be irritating to some tissues.

Tetracycline is an antibiotic whose mechanism of action is to bind to the 30S ribosomal subunit, thereby inhibiting protein synthesis. It has broad activity but is only bacteriostatic against some bacteria. It is effective against certain protozoa. Resistance is commonly seen for many bacteria when tetracycline is administered. Tetracycline chelates calcium and as a result can affect bone and teeth formation. The calcium chelation causes enamel dysplasia and tooth discoloration ("tetracycline teeth"), skeletal deformities, and inhibition of bone growth. Tetracycline is the wrong drug for use in young animals.

Trimethoprim + sulfonamide act synergistically on bacteria and have a broad spectrum of activity. The mechanism of action comes from competition with *para*-aminobenzoic acid for the enzyme that synthesizes dihydrofolic acid in bacteria. For many bacteria, it is bacteriostatic. Trimethoprim + sulfonamide combinations can cause keratoconjunctivitis sicca (KCS), skin reactions, anemia, thrombocytopenia, and allergic reactions including type II and III hypersensitivities, and arthropathies. It is not recommended in young animals and Doberman Pinschers. Dogs may be more sensitive than other species to sulfonamide reactions because they lack the ability to acetylate sulfonamides to other metabolites.

Chloramphenicol is an antimicrobial drug capable of inhibiting bacterial protein synthesis via binding to the ribosome. This antibiotic molecule can cause bone marrow suppression at high dosages or with prolonged use. Cats appear particularly sensitive to the effects of this drug. Bone marrow suppression has been seen in cats after only 14 days of treatment. Chloramphenicol should not be used in pregnant animals, neonates, or cats. It is appetite suppressive and can pose a risk of toxicity in humans. Exposure to small dosages has caused anaplastic anemia in people. There are safer, better drugs for use in neonates.

Ivermectin is an antiparasitic avermectin. These molecules are macrocyclic lactones that originally were produced from molds. These drugs are neurotoxic to parasites by potentiating glutamate-gated chloride ion channels in the parasites. Paralysis and death of parasites are caused by increased permeability to chloride ions and hyperpolarization of nerve cells. Toxicity can occur at high dosages and in breeds where ivermectin crosses the blood-brain barrier. Ivermectin should not be given to pregnant animals or those younger than 6 weeks of age. Ivermectin at doses of 400 μg/kg has produced toxicosis in kittens and doses as low as 300 μg/kg have been lethal in young cats.

All aspects of disposition of drugs by an organism, absorption, distribution, metabolism, and excretion are affected by the age and maturity of the animal. As a result, newborn patients are much more susceptible to the adverse effects of drugs, since their various physiologic pathways governing metabolism of drugs are so immature. In neonates, the permeability of the intestinal mucosa is increased and as a result the uptake of toxic molecules is increased. Newborn animals also have decreased concentration of plasma proteins the first few weeks of life, which can lead to more unbound compound and a potentially longer plasma half-life and toxic action. Young animals have less total body water and more extracellular fluid than adults, which can lead to a longer half-life of toxic molecules. Furthermore, younger animals have decreased body fat. This results in less accumulation of lipid soluble molecules in the fat and thus persistently increased plasma levels of the drug. Because of increased skin hydration, the newborn animal has greater capacity for percutaneous absorption of molecules. As a result, the pediatric patient is at much higher risk for the significant cutaneous absorption of potentially toxic molecules. Finally, volatile gases are more rapidly absorbed from the pediatric respiratory tract than from adults. As a result, young animals are more sensitive to the potential toxic effects of inhaled gases.

Plasma protein concentration is much lower in pediatric animals, particularly glycoproteins and albumin. With less potentially toxic drug plasma-bound, the risk of toxicity increases as the concentration of free pharmacologically active compound rises. If a substance has a narrow therapeutic index and is highly protein bound, these age-related changes become significant and may make intoxication more likely to occur. Thus increased unbound toxic compounds may have longer access for free distribution to outlying tissues.

Neonates also display differences in regional organ blood supply. Differences in renal blood flow can result in wide alterations in drug or toxin excretion. Pediatric patients have proportionally greater blood supply to the heart and brain, increasing the risk of toxic effects from lower exposures to cardiac and CNS poisons. Newborns have increased permeability of the blood-brain barrier. Consequently, younger animals have increased potential for toxic exposure to CNS intoxicants. Thus, the CNS, normally more protected in adults, is at much higher risk of exposure to toxins in the neonatal animal.

Neonatal animals show incomplete hepatic metabolism and reduced renal excretion. As a result, elimination and clearance of potentially injurious molecules are reduced. Young animals show both reduced phase I (oxidative) and phase II (glucuronidation) reactions. Puppies may not show phase I activity until day 9 after whelping; this activity increases after day 25 until it reaches adult activity levels at day 135. Since hepatic drug metabolism is decreased, plasma clearance of drug is decreased, plasma half-life is increased and the compound may obtain toxic concentrations as a result. Until the liver matures, great care must be taken in prescribing drugs and prevention of toxic exposure.

Neonates demonstrate a steady increase in glomerular filtration and renal tubular function in the weeks after birth. Young animals have reduced renal excretion, decreasing clearance of renally excreted compounds and the products of hepatic phase II metabolism. In puppies, adult levels of glomerular filtration and tubular function are achieved by 10

TABLE 6-3 **Drug metabolism and considerations in neonates**

Drug	Considerations
Renally excreted antimicrobials (penicillin, ampicillin, cephalosporins, fluoroquinolones, aminoglycosides)	Caution if given to neonates
β-Lactam antibiotics	Antimicrobial drug of choice Half-life is prolonged Large therapeutic index
NSAIDs	Require hepatic metabolism Risk of renal injury from NSAIDs is greatly increased Not recommended in neonates

NSAIDs, Nonsteroidal antiinflammatory drugs.

weeks of age. Until then, water-soluble compounds have decreased clearance and extension of plasma half-life. One can anticipate even greater toxic effects in sick or dehydrated neonatal animals in which the kidneys are even further compromised (Table 6-3).

The neonate is a fragile and complex organism rapidly changing into an adult. The practicing clinician must be aware of this transition and the unique physiologic traits of young animals and make appropriate concessions to successfully treat and manage the pediatric patient.

VACCINATIONS (see Chapter 14)

In recent years, vaccination protocols and specific vaccinations have come under increased scrutiny. Duration of immunity for various vaccines and the potential deleterious effects of certain vaccines brought the whole rationale for vaccinating into question. Nevertheless, infectious diseases are still very much present that prey on the pediatric patient. Vaccinations should be administered only if the risk of an individual animal being exposed to a particular infectious agent has been rigorously considered. Furthermore, criteria, such as health risk associated with infection, actual disease incidence and severity, and vaccine efficacy, must likewise be assessed. "Core" vaccines are those immunizations that have been recommended to be administered to *every* dog and cat who is 6 months of age or younger or is not known to have had any prior vaccination. These vaccines have been deemed necessary because the diseases they prevent display significant morbidity and mortality, are widely distributed, and/or may have zoonotic potential. "Noncore" vaccines are those influenced by geographic distribution of the infectious agent, age of the patient, and lifestyle of the animal (indoor only vs. free-roaming). Noncore vaccines are those recommended against less common or less severe diseases and against those that are either self-limiting or lend themselves well to treatment. The veterinarian has a tremendous responsibility to the animal, its caretakers, and to the American public in selecting safe and effective vaccines for young animals.

Any recommendations for vaccinations of puppies and kittens must be recognized as recommendations. Nevertheless, they are guidelines based on the most recent studies and research and the best understanding of the most current, available science concerning immunization. Certainly, there are risks inherent in vaccinating. However, vaccines represent one of the best bargains for animal health care based on their efficacy, cost, and overall safety. Vaccine selection is the responsibility of the veterinarian providing care and must be a serious decision based on determination of the animal's risk of exposure and its lifestyle and age. The decision must reflect the geographic incidence of the disease in question, its relative morbidity and mortality, the animal's overall health, and potential of the disease for transmission to human beings.

For dogs, the Task Force recommends as "core" vaccines, immunization against canine distemper virus (CDV), canine parvovirus (CPV), canine adenovirus-2 (CAV-2), and rabies. When possible, modified-live virus (MLV) vaccines are recommended over killed vaccines. Killed rabies vaccines (determined to be either 1- or 3-year vaccines) are the only types available at present within the United States and most other countries. A minimum of three doses of "core" vaccines (CDV, CPV, and CAV-2) should be given to puppies between 6 and 16 weeks of age. The final dose must be administered between 14 and 16 weeks of age. A subsequent inoculation of the core vaccines should be given 1 year after the administration of the last in the puppy series. A single rabies immunization is recommended at 16 weeks of age. This is followed up with a single injection rabies booster 1 year later.

"Noncore" vaccines for canines include *Bordetella bronchiseptica* vaccines, distemper-measles, parainfluenza virus vaccines, *Borrelia burgdorferi*, *Lyme borreliosis,* and *Leptospira interrogans* (all four serovars).

Nonrecommended canine pediatric vaccines include measles, coronavirus, canine adenovirus-1, and *Giardia* vaccine. Veterinarians must become familiar with recommended and nonrecommended vaccines, incidence of a particular disease in an area, frequency of administration of vaccines, type to be administered (killed vs. avirulent live), and route of administration (topical vs. parenteral).

For years the primary vaccination series in cats for core immunizations was a dose administered at 9 and 12 weeks. Currently, recommended feline guidelines are first dose of core vaccines (feline parvovirus [panleukopenia virus], herpes virus-1, and calicivirus) be administered as early as 6 weeks and then given every 3 or 4 weeks until 16 weeks of age. A booster of these components should follow in 1 year. A rabies vaccine (also considered a core immunization for cats) can be administered as early as 12 weeks of age. A rabies booster is recommended 1 year later.

At present, chlamydiosis, feline leukemia virus (FeLV) vaccine, and vaccinations for *Bordetella bronchiseptica* are not listed as feline core vaccines and should be given only if exposure risk is great. Furthermore, vaccination for feline immunodeficiency virus (FIV), feline coronavirus (FCOR) to protect against feline infectious peritonitis (FIP), and *Giardia lamblia* are generally not recommended at all.

Vaccinations are potent biologic agents created to prevent disease. As with any foreign substance administered to a living system, vaccines have the potential for adverse reactions. Vaccinations must meet United States Department of Agriculture (USDA) standards guaranteeing their safety, efficacy, potency, and purity. Nevertheless, even by requiring vaccines to meet these standards there still exists the possibility for adverse vaccine reactions. Some reactions may be seen more often with certain agents, others have increased frequency in certain breeds, and others are simply idiosyncratic and unpredictable. Clinical signs of vaccine reactions can include anorexia, pyrexia, and malaise for 1 or 2 days after the immunization. Most of the reactions are mild, self-limiting, and require little or no treatment. However, any reaction to a vaccine must be documented in the animal's legal record to protect against further incidents.

Reactions to vaccines may manifest themselves in a variety of ways. Feline injection site sarcomas or fibrosarcomas develop secondary to inflammation of the vaccination site. Certain adjuvants and other ingredients have been implicated with an increased risk of development of these tumors. Clinicians are encouraged to avoid multiple vaccines in the same site to decrease the amount of inflammation at the site and to administer only vaccines for diseases for which the animal is actually at risk. The "three-two-one" rule advocated by the Vaccine-Associated Feline Sarcoma Task Force (VAFSTF) is very helpful. It states that persistent swellings in areas of recent vaccination should be rigorously monitored. The "rule" maintains that if the swelling persists for 3 months or more, if the area is larger than 2 cm in diameter, or if the size of the swelling increases after 1 month and if any of the criteria are met, the swelling should be biopsied and samples sent out to a board-certified pathologist.

Type I hypersensitivity to vaccination is known as *anaphylaxis* or *immediate hypersensitivity* and is mediated by the IgE antibody. In this instance, the animal's immune system is reacting to adjuvants, preservatives, or the antigen contained in the vaccine. Typically, these reactions occur within 2 to 3 hours of vaccination. In dogs, most commonly seen signs are angioedema, urticaria, and pruritus, but symptoms can be worse and include respiratory collapse and full-blown anaphylaxis. For cats, the acute onset of vomiting and diarrhea, with associated hypovolemia, and respiratory and vascular collapse may be seen. Any animal showing these signs within hours of being vaccinated should be returned to the hospital immediately for thorough examination and perhaps emergency medical therapy and support. The animal's medical record should be flagged inside and out to prevent future incidents of this type and caretakers should be advised to never give this product again.

Type II hypersensitivities to vaccines (autoimmune reactions) have been reported to occur in dogs. Some reports maintain that immune-mediated hemolytic anemia and immune-mediated thrombocytopenia can develop shortly after a recent vaccination. Animals developing either condition within a month of receiving an immunization should be protected from subsequent use of that vaccine product.

Type III hypersensitivities are immune complex reactions. Anterior uveitis associated with the use of the CAV-1 vaccine and the complement-mediated rabies vaccine-induced vasculitis or dermatitis in dogs are examples of this adverse vaccine reaction.

Type IV hypersensitivity reactions are the cell-mediated responses, which can occur locally or systemically. Examples of type IV reactions include sterile granulomas at vaccine sites and polyradiculoneuritis.

Despite recent findings concerning deleterious effects of certain vaccines, vaccinations still remain one of the clinician's greatest weapons in preventing disease. Vaccines have played an incredible role in providing better health for generations of kittens and puppies. The clinician must balance the risk of disease to the animal presented against the risk of potential adverse side effects. We must also convey to the owner the comparative risks of overvaccinating vs. undervaccinating.

FADING PUPPIES (see Chapter 11)

Many neonatal losses are often ascribed to the "fading puppy syndrome." Sadly, many times any cause of death in newborns is lumped into this category. True fading puppy syndrome is believed to be caused by neonatal septicemia. Confirmation of a septic process may require histologic determination, evaluation of cultures, and identification of specific agents. Nevertheless, effective therapy for this condition must never wait for laboratory results. Aggressive therapy must be initiated early to help affected pups. Because of a neonate's minimal energy reserves, an immature immune system, and small size, neonatal septicemia can progress rapidly and quickly lead to death. Factors that can lead to neonatal septicemia include maternal infections (e.g., endometritis, metritis, mastitis), contaminated environments (puppy mills, veterinary hospitals, and boarding kennels), antimicrobial drug treatment (any drug that causes reduction in the number of anaerobic bacteria in the GI tract), feeding formulas with excessive osmolarity (the bitch's milk is best because it is high in IgA), stress (e.g., tail docking, dewclaw removal), and chilling puppies (causes reduction in transformation of lymphocytes).

Clinical signs of neonatal septicemia are found in Box 6-3. Sloughing is believed caused by hypoxia, reduced blood supply to extremities in already hypovolemic newborns, and a vasculitis directly caused by the infectious organism.

Treatment for affected puppies involves selection of an antibiotic with a wide spectrum of activity that is at the same time safe for the young animals. *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus intermedius,* and β-hemolytic streptococci are some of the more frequently observed microorganisms. Cephalosporins can be used safely in such

BOX 6-3 Clinical signs of neonatal septicemia

- Weakness
- Failure to suckle
- Vocalization
- Diarrhea
- Cyanosis
- Coma
- Occasional sloughing of extremities (toes, tails, ears)

puppies. Selection of safe antibiotics and safe dosages and intervals are considered elsewhere in this discussion and in Chapter 27.

NUTRITIONAL CONSIDERATIONS (see Chapters 8 and 44)

Proper nutrition is essential for the health of the neonate. Inadequate caloric intake must be addressed promptly to prevent serious consequences. Sick pups who fail to nurse on their own may need to be bottle fed or tube fed (see Chapter 9). Newborns separated from their mothers must be kept warm. Hypothermia retards digestion and promotes GI ileus. This loss of GI motility is often present in septicemic pups.

For bottle feeding, a human infant bottle with a soft nipple is used. Healthy neonates should be bottle fed four times a day. Bottle-fed pups take longer to feed but consume more than tube-fed pups. The stomach distends gradually during bottle feeding, allowing the newborn to eat more. Since they consume more at each feeding, bottle-fed pups require fewer feedings than tube-fed counterparts. Tube feeding is done using a 5 Fr red rubber catheter for neonates under 300 gm and 8 to 10 Fr for larger neonates. Tube feeding should be done only by experienced personnel. Overdistention is easy to do and can result in regurgitation and respiration pneumonia. Improper tube placement into the trachea is easily done in neonates since no gag reflex develops until approximately 10 days of age. Overfeeding is much more likely to occur by tube feeding and it can be particularly harmful to cold puppies when ileus may be present. Tube feeding bypasses the suckle response and tube-fed pups may suckle on the vulvas, prepuces, and extremities of siblings, resulting in a moist dermatitis.

For normal neonates, less than 10% of the body weight is lost within the first 24 hours of life (loss of more than 10% greatly decreases survival rates). Healthy puppies and kittens should start to grow and double their weight by 10 days after their birth. Formula-fed neonates (via bottle or tube) grow at significantly slower rates than healthy siblings despite identical caloric intake. However, after weaning and receiving the same growth diets, normal nursing and formula-fed pups reach identical weights. In general, formula-fed pups should increase their body weight at least 10% each day during the first 3 weeks of life. Daily monitoring of the weight of newborns becomes critical and should be done on a gram scale three times daily.

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